2012

Does the Use of an Oral Lipase Inhibitor (Orlistat) Increase Appetite?

Sandra Boyd
Philadelphia College of Osteopathic Medicine, sandrabo@pcom.edu

Does the Use of an Oral Lipase Inhibitor (Orlistat) Increase Appetite?

Sandra L. Boyd, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences-Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Medicine
Philadelphia, Pennsylvania

16 December 2011

Abstract

OBJECTIVE: To determine whether or not Orlistat ingested prior to a meal causes an increased appetite response.

STUDY DESIGN: A Review of three randomized controlled trials studies from 2003-2008 that were in the English language.

DATA RESOURCES: Randomized controlled trials comparing the effect of Orlistat on satiety were found using PubMed, OVID, and Cochrane databases.

OUTOMES MEASURED: Outcomes measured in the studies were: sensation of appetite, hunger, fullness, nausea, bloating, heartburn, belching, epigastric burning, and prospective food consumption. Each study measured individual patient responses using a VAS (visual analogue scale). Demarchi et al (2004) used a gastric barostat to measure gastric distention and accommodation to a meal. Both Demarchi (2004) and Goedecke et al (2003) measured plasma CCK levels and Ellrichmann et al (2008) measured gherlin, GLP-1, and PYY in addition to CCK. In addition, Ellrichmann et al (2008) used an ultrasound to determine changes in gallbladder size, and gastric emptying using a C sodium-Octanoate breath test.

RESULTS: Results from both the Demarchi (2004) and Goedecke et al (2003) studies did not demonstrate any significant increase in appetite or inhibition of anorexogenic hormones with Orlistat treatment prior to a test meal. The Ellrichmann et al (2008) results demonstrated decreased gallbladder contractility, increased appetite and food consumption.

CONCLUSIONS: The results of whether Orlistat ingested prior to a meal causes an increased appetite response has not been shown in two of the three studies reviewed. Future tests should include varied fat concentrations in a diet and administered to the same subjects with testing trials in longer duration. Orlistat is still an effective dietary aid in the battle against obesity in today's society.

KEY WORDS: Orlistat, appetite, satiety, diet, obesity, treatment, intervention, weight loss

Introduction

Overweight and obesity is a preventable disease that is associated with significant increases in both morbidity and mortality. Overweight is defined as having a BMI over 25 and obesity is having a BMI over 30. Over 68% of adults in the US are overweight,[4] and about one-third of U.S. adults (33.8%) are obese.[1] These statistics place obesity and overweight one of the most common medical conditions in every field of practice. Non-Hispanic black women and Hispanics have the highest rates of obesity (41.9% and 30.7%)[1].

The conditions also impose an additional cost. On average, people who are considered obese pay $1,429 (42 percent) more in health care costs than normal-weight individuals.[1] The total cost due to obesity in the US is estimated to be $117 billion.[5] Physician office visits related to obesity totaled 62.7 million in 2008.[5] A majority of additional costs entailed by the patient may be due to the complications of obesity such as reproductive, endocrine, gastrointestinal, cardiovascular, pulmonary, and conditions such as dyslipidemia, metabolic syndrome, cancer, insulin resistance and Type 2 diabetes.[2]

The cause of overweight and obesity come from energy imbalance, and there is no single cause of obesity. In addition, genetic, environmental, behavioral, and socioeconomic factors can all lead to overweight and obesity. Body weight regulation has both a neural and endocrine component that effect energy intake and output. Treatment for the condition is centered on these two components. Behavioral and dietary lifestyle modifications with a focus on less calories, fat and sugar, along with exercise is the treatment of choice and has the most success long-term.[5] Other treatments include pharmacologic such as a lipase inhibitor, appetite suppressants (adrenergic or norepinephrine/serotonin reuptake inhibitor), and bariatric surgery.

Appetite and satiety is influenced by many factors that are integrated by the brain, most importantly in the hypothalamus.[3] Hormones, neural afferents, and metabolites may influence the hypothalamic center. Gut peptide hormones such as ghrelin (from stomach to influence feeding), glucagon-like peptide-1-(7-36)-amide (GLP-1), peptide YY (PYY), and cholecystokinin (a.ka. CCK, which is produced in the small intestine) all influence appetite via the vagus nerve. When there is adequate digestion of dietary triglycerides by pancreatic lipase to produce FFAs (Free Fatty Acids) anorexigenic hormones, CCK, GLP-1, PYYare released, which in turn, will increase satiety. In addition, CCK levels directly influence gallbladder emptying

Americans spend $33 billion annually on weight-loss products and services.[5] Several weight-loss products and services are available in the US market, and diet pills are a popular choice. One of them is Orlistat which is a lipase inhibitor. A pharmaceutical agent Orlistat, is the only FDA approved drug to prevent fat absorption in the body. A proposed theory is that Orlistat accelerates gastric emptying, and inhibits gallbladder motility with reduced secretion of GLP-1, PYY and CCK. . Therefore, Orlistat may actually cause an increase in appetite and potentially cause weight-gain, or unchanged weight status. This paper evaluated three randomized controlled studies (single blind, double blind) comparing the use of a lipase inhibitor to a placebo in appetite after an ingested meal.

Objective

The objective of this selective EBM review is to determine whether or not Orlistat ingested prior to a meal causes an increased appetite response.

Methods

The studies included healthy non-obese men and women aged 19-32 who were pre-prandial and given Orlistat 120 mg prior to a meal. Included in this analysis were a double-blind randomized crossover design which compared a five-day regimen of Orlistat 120 mg tablet three times daily pre-prandial each meal against a visually matched placebo 120 mg; a randomized, single-blind, placebo-controlled, crossover trial which compared Orlistat 120 mg tablet against a visually matched placebo 120 mg ingested with a test meal; and a randomized, single-blind, placebo-controlled, crossover trial which compared Orlistat 120 mg tablet against a visually matched placebo 120 mg (2 g flour) ingested with a high fat meal after an overnight fast. See **Table 1** for an outline of the patient demographics and characteristics.

Research sources used were PubMed, OVID, and Cochrane databases. Articles for this systemic review were located by key words “orlistat”, “satiety”, “appetite”, and “weight loss”. All articles were published in English, in peer reviewed journals, were selected based on the importance of outcomes and relevance to patients. Inclusion criteria included randomized controlled, double blind, single blind, cross-over trials involving healthy non-obese individuals (BMI<30) aged 19-32. Studies excluded were outcomes not patient oriented such as hormone and enzyme level responses. To successfully measure patient outcomes, the following statistical methods were utilized: r^2, p-values, AUC, ANOVA, and α level.

Table 1 – Demographics and Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Goedecke[6] 2003	Randomized, single-blind, placebo-controlled, crossover trial	19	Mean age 21±1.6y	• BMI:<30kg/m^2 • Absence of known metabolic conditions • No medications for chronic conditions	• Obese pts. w/ BMI>30	0	(2) Randomized trials separated by 2 wks. where subjects ingested test meal w/ Orlistat (120mg) or placebo (2g flour)
Demarchi[7] 2004	Double-blind randomized cross-over design	18	Mean age 24±1.11y[18-32]	• Healthy pts. with no pre-existing medical condition	• Currently on medication • Symptoms or history of gastrointestinal disease • Drug allergies • Major abdominal surgery	0	(5) day regimen of 120 mg Orlistat tablet three times daily pre-prandial each meal and a visually matched placebo
Ellrichmann[8] 2008	Randomized, single-blind, placebo-controlled, crossover trial	25	20-32 years	BMI in normal range 19.1-25.0 kg/m^2	• History of GI or endocrine disorders	0	Oral dose of Orlistat 120 mg ingested with a test meal after an overnight fast

Outcomes Measured

Each study measured individual responses using a VAS (visual analogue scale) and each study measured a variety of outcomes. Goedecke et al had patients mark their appetite sensation on a 100 mm line from “not at all full” (0mm) to “extremely full” (100 mm). Ellrichmann et al measured the effects of Orlistat on sensation of appetite, hunger, fullness, and prospective food consumption.

Demarchi et al had patients rate gastrointestinal sensation of fullness including bloating, nausea, heartburn, belching, epigastric burning, discomfort and satiety. There were two test

periods with the test duration of 5 days and a washout period of 3 weeks. In addition, sensitivity to gastric distention and accommodation to a meal was measured using a gastric barostat. Venous blood samples were taken before and after a meal at timed intervals to measure plasma CCK. Satiety was measured using a VAS with an interval of 5-43 days. During the satiety test, the patients scored sensations every 5 minutes.

Goedecke et al completed two randomized trials with a recovery period of 2 weeks between each trial. Satiety and hunger were measured along with blood sampling for CCK levels pre-prandial and every hour after a test meal for 4 hours. Patients rated motivation to eat such as hunger, satiety, fullness and prospective consumption prior to a meal and every hour up to 4 hours post meal using a VAS. At 4 hours post-prandial, the patients were given lunch with no limits on quantity based on their appetite.

Ellrichmann et al trial was conducted on two separate trials. Plasma concentrations of gherlin, GLP-1, CCK, and PYY were obtained pre-prandial and 2 hours postprandial. Ultrasound measurements were used to determine Gallbladder size 120 minutes post-prandial, and gastric emptying was measured using a C sodium-octanoate breath test. A visual analog scale was used at 15-minute intervals over a period of two hours after ingestion of a meal.

Results

In the Ellrichman et al (2008) study, the administration of Orlistat led to significant inhibition of gallbladder contractility. In addition, the rise in postprandial plasma concentrations of GLP-1, PYY, and CCK was significantly lower after Orlistat administration. The mean satiety ratings were reduced by 15% after Orlistat treatment and fullness was lowered by 12%. Orlistat treatment caused a significant increase in appetite (24%) and prospective food consumption (31%). There was a linear relationship between gallbladder emptying and the plasma levels of

CCK, PYY, and GLP-1. A decrease in gallbladder contractility decreased levels of the plasma anorexigenic hormones. In addition, there was positive correlation between the ratings of satiety and fullness and gallbladder emptying, and hunger and food consumption were inversely related. There was statistical significance between satiety and incremental concentrations of CK (r^2=0.41, P<0.0001) and GLP-1 (r^2=0.14, P=0.0064). The rise in postprandial plasma concentration of GLP-1, PYY, and CCK was significantly lower after Orlistat administration.[8] The statistical significance is demonstrated in **Table 2**.

Table 2: One-Way ANOVA statistical analysis of GLP-1, PYY, CCK and Ghrelin plasma concentrations placebo vs. administration of Orlistat[8]

Hormone	Differences Between Experiments	Differences Over Time	Differences due to Interaction of Experiment and Time
GLP-1	p=0.015	p<0.0001	p=0.002
PYY	p=0.16	p<0.0001	p<0.001
CCK	p<0.0001	p<0.0001	p<0.0001
Ghrelin	p= 0.77	p<0.0001	p=0.18

In the Goedecke et al study, Orlistat was not shown to alter the ratings of hunger, satiety, prospective consumption or fullness while examining changes over time (**Table 3**). There were no differences in post-test meal intake between the Orlistat and placebo trials. The plasma CCK response showed no significant difference in response to the high-fat meal with Orlistat compared to placebo administration. However, the study showed variability in CCK administration due to variability in body fatness. BMI correlated negatively with plasma CCK for both the Orlistat and placebo trials (R=-0.690, P=0.001 and R=-0.649, P=0.003 respectively

Table 3: Area under the curve for appetite scores in response to the high-fat test meal with Orlistat and placebo administration[6]

	Orlistat	Placebo	P-value
Hunger (mm x 4hrs)	14,866 ±5324	15,021 ±5376	0.848
Satiety (mm x 4 hrs)	13,378 ±4626	13,208 ±5516	0.755
Fullness (mm x 4hrs)	6,898 ±3422	7,675 ±4293	0.360
Prospective Intake (mm x 4 hrs)	16,697 ±4259	16,631 ±4081	0.924

In the Demarchi et al double-blind, randomized, crossover study, sensitivity to gastric distension and gastric accommodation to a meal was studied using a gastric barostat. Two test periods of 5 days each were completed. The fasting perception and discomfort thresholds during fasting distentions with Orlistat did not differ significantly from the placebo. The area under the curve (AUC) of perception scores during fasting isobaric distentions with the placebo and the Orlistat pre-treatment showed no significant differences as outlined in **Table 4**.

Table 4: Area under the curve of perception scores in response during fasting isobaric gastric distentions with placebo and Orlistat pre-treatment[7]

	Placebo	Orlistat
Fullness	70±11	80±9
Bloating	81±12	78±10
Satiety	76±16	75±10
Discomfort	78±10	77±11
Belching	44±12	28±7
Nausea	35±13	23±8
Epigastric burning	66±11	64±10
Heartburn	42±13	31±10

During postprandial distentions the postprandial pressure-volume curves did not differ between both treatment groups. In addition, treatment with Orlistat, first perception and discomfort thresholds were not significantly altered as outlined in **Table 5**.

Table 5: Area under the curve (AUC) of perception scores during postprandial isobaric gastric distentions, with placebo and Orlistat pre-treatment (no significant differences)[7]

	Placebo	**Orlistat**
Fullness	94±13	70±11
Bloating	95±13	70±11
Satiety	98±14	70±13
Discomfort	97±13	70±11
Belching	47±18	70±10
Nausea	54±16	70±13
Epigastric burning	63±13	70±12
Heartburn	37±13	70±12

Serum CCK analysis after Orlistat pre-treatment demonstrated lower levels when compared to the placebo. CCK levels, P=0.09, and preprandial AUC, P=0.06. In post-prandial CCK levels ($P<0.01$) and the postprandial AUC (P=.0.3) were significantly lower after orlistat pre-treatment. A satiety test both after the placebo and Orlistat treatments showed a high correlation between satiety scores and the amount of calories ingested ($R>0.95$, $P<0.0001$). Pre-treatment with Orlistat did not significantly alter the amount of calories ingested until maximum satiety as compared to placebo shown in **Table 6**.

Table 6: Area under the curve (AUC) of perception scores during the satiety drink test, with placebo and orlistat pre-treatment[7]

	Placebo	Orlistat
Fullness	207±15	190±13
Bloating	160±21	149±17
Satiety	148±11	135±10
Discomfort	119±24	140±19
Belching	76±14	87±17
Nausea	61±11	55±16
Epigastric burning	40±10	59±15
Heartburn	27±8	34±10

Discussion

The articles used in this EBM review demonstrate that the control of gastric sensitivity and gastric accommodation to a meal is incompletely understood[7]. Lipid digestion and subsequent release of CCK and activation of CCK B receptors are key factors in gastric emptying and sensitivity.

There were contradictory findings between the studies that examined to effects of Orlistat on satiety. Both the Demarchi et al (2004) and Goedecke et al (2003) did not demonstrate findings that an oral lipase inhibitor, Orlistat, would significantly reduce plasma CCK release to influence gastric sensitivity with sensation of hunger or satiety in response to a meal. Although lowered CCK levels were observed with Orlistat pre-treatment prior to a meal in these studies, the medication had no effect on calories consumed, gastric distention, and failed to elicit any symptoms of increased appetite.

On the other hand, Ellrichmann (2008) did show increased appetite with the administration of Orlistat with the relationship of inhibition of CCK, GLP-1, and PYY release. The tests

demonstrated Orlistat accelerates gastric emptying. Ghrelin, another anorexigenic hormone, was unaffected. The experimental testing took place for up to 120 minutes only versus the other studies consisted of a longer length time period for testing.

Conclusion

Two of the three studies reviewed demonstrate overall, that the use of Orlistat does not cause an increase in appetite in healthy patients. One study showed an increase in appetite but the study duration was a shorter time period limited to just 2 hours which places the validity of the study in question. The response to symptoms related to satiety was subjective using the VAS and were subject to potential varied responses based on the patient's tolerance and interpretation. In addition, varied results between the studies may also be directly correlated to the diet the patients were given, where fat content plays an important role in measuring the body's response. Future studies could include varied amounts of fat content in test meals and measure responses in both anorexigenic hormones and subjective ratings by the patients.

If continued to use as directed, Orlistat can be an effective weight loss regimen adjunct to healthy lifestyle changes.

References

1. Overweight and Obesity. Centers for Disease Control and Prevention Website. http://www.cdc.gov/obesity/data/adult.html. Accessed September 27, 2011.

2. Kanaya AM, Vaisse C. Chapter 20. Obesity. In: Gardner DG, Shoback D, eds. Greenspan's Basic & Clinical Endocrinology. 9th ed. New York: McGraw-Hill; 2011.

3. Flier JS, Maratos-Flier E. Chapter 77. Biology of Obesity. In: Longo DL, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, Fauci AS, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2011.

4. Overweight and Obesity Statistics. Weight Control Information Network Website. http://win.niddk.nih.gov/statistics/. Accessed September 29, 2011.

5. Statistics Related to Overweight and Obesity. Weight Loss and Obesity Resource Center Website. http://www.weightlossobesity.com/obesity/overweight-and-obesity-statistics.html. Accessed October 1, 2011.

6. Goedecke J, Barsdorf M, Beglinger C, Levitt N, Lambert E. Effects of a lipase inhibitor (Orlistat) on cholecystokinin and appetite in response to a high-fat meal. *International Journal of Obesity & Related Metabolic Disorders* [serial online]. December 2003;27(12):1479-1485.

7. Demarchi B, Vos R, Deprez P, Janssens J, Tack J. Influence of a lipase inhibitor on gastric sensitivity and accommodation to an orally ingested meal. *Alimentary Pharmacology & Therapeutics* [serial online]. June 15, 2004;19(12):1261-1268.

8. Ellrichmann M, Kapelle M, Meier J, et al. Orlistat inhibition of intestinal lipase acutely increases appetite and attenuates postprandial glucagon-like peptide-1-(7-36)-amide-1, cholecystokinin, and peptide YY concentrations. *The Journal Of Clinical Endocrinology And Metabolism* [serial online]. October 2008;93(10):3995-3998.